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(54) Title: INTEGRIN ANTAGONISTS

(57) Abstract

This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor antagonists. The vitronectin receptor antagonist compounds of the present invention are $\alpha v\beta 3$ antagonists, $\alpha v\beta 5$ antagonists or dual $\alpha v\beta 3/\alpha v\beta 5$ antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation and tumor growth.

9/916,977

WHAT IS CLAIMED IS:

1. A compound of the formula

X-Y-Z-Ring-A-B

wherein:

Ring is a 4 to 10-membered mono-or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S, and either unsubstituted or substituted with R^{27} and R^{28};

X is selected from

$-NR^1R^2$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-R^3$, $-\overset{\overset{NR^2}{\|}}{C}-NHR^4$, $-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$,

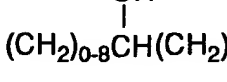
$-aryl-NR^1R^2$, $-aryl-\overset{\overset{NR^1}{\|}}{C}-NR^2R^3$, $-aryl-NR^1-\overset{\overset{NR^2}{\|}}{C}-NR^3R^4$,

or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^{13}, R^{14}, R^{15} or R^{16};

Y is selected from

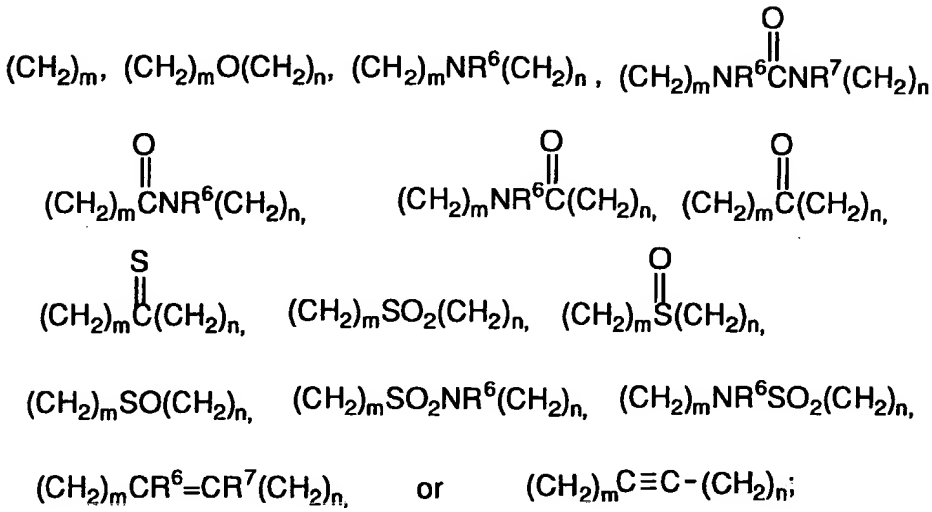
C_{0-8} alkylene,
C_{3-10} cycloalkyl,
C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,
C_{0-8} alkylene-$CONR^5$-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-$S(O)_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,

$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NR^5-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-NR^5-CO-$(CH_2)_{0-6}$, or



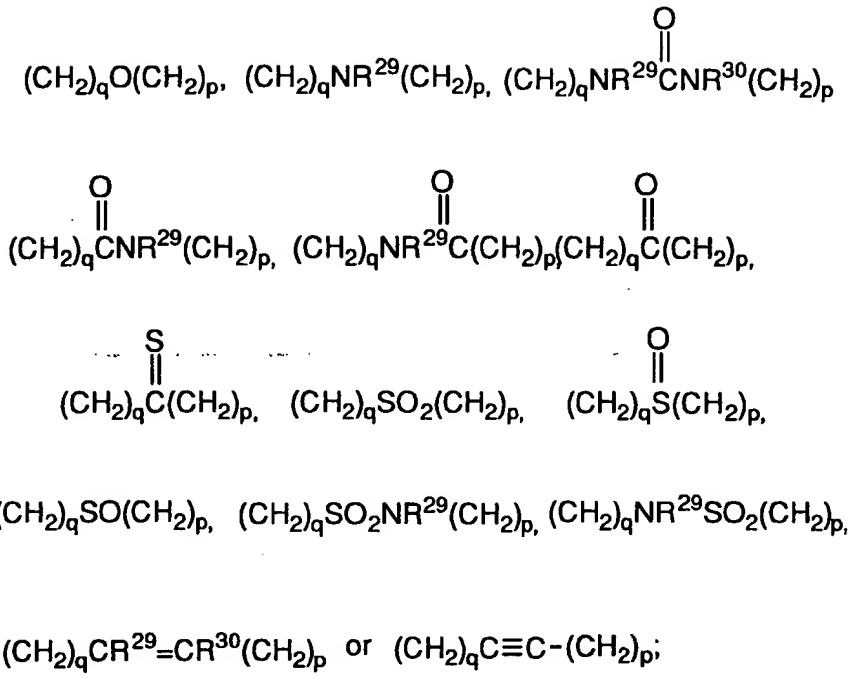
;

Z is selected from



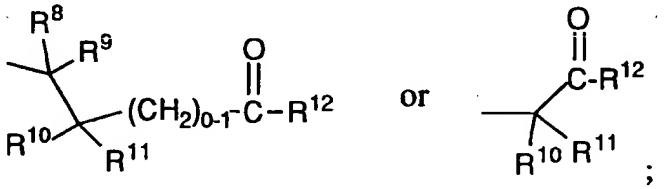
where m and n are each independently an integer from 0 to 6;

A is selected from



where p and q are each independently an integer from 0 to 6;

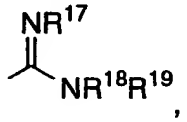
B is selected from



R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29} and R^{30} are each independently selected from

hydrogen,
halogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,

C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,



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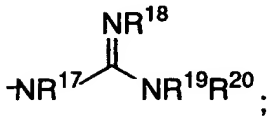


;

R^8 and R^9 are each independently selected from
hydrogen,
aryl,
halogen,
aryl-$(CH_2)_p$-,
hydroxyl,
C_{1-8} alkylcarbonylamino,
aryl C_{1-5} alkoxy,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{1-8} alkylaminocarbonyl,
C_{1-6} alkylcarbonyloxy,
C_{3-8} cycloalkyl,
amino,
C_{1-6} alkylamino,
amino C_{1-6} alkyl,
arylaminocarbonyl,

aryl C_{1-5} alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl C_{1-6} alkyl,
hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl, either unsubstituted or substituted, with one or more groups selected from: halogen, hydroxyl, C_{1-5} alkylcarbonylamino, aryl C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, aminocarbonyl, C_{1-5} alkylaminocarbonyl, C_{1-5} alkylcarbonyloxy, C_{3-8} cycloalkyl, oxo, amino, C_{1-3} alkylamino, amino C_{1-3} alkyl, arylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, aminocarbonyl, aminocarbonyl C_{1-4} alkyl, hydroxycarbonyl, or hydroxycarbonyl C_{1-5} alkyl,
$HC{\equiv}C(CH_2)_r$ -
C_{1-6} alkyl-$C{\equiv}C(CH_2)_r$ -,
C_{3-7} cycloalkyl-$C{\equiv}C(CH_2)_r$ -,
aryl-$C{\equiv}C(CH_2)_r$ -,
C_{1-6} alkylaryl-$C{\equiv}C(CH_2)_r$ -,
$H_2C{=}CH(CH_2)_r$ -,
C_{1-6} alkyl-$CH{=}CH(CH_2)_r$ -,
C_{3-7} cycloalkyl-$CH{=}CH(CH_2)_r$ -,
aryl-$CH{=}CH(CH_2)_r$-,
C_{1-6} alkylaryl-$CH{=}CH(CH_2)_r$ -,
C_{1-6} alkyl-$SO_2(CH_2)_r$-,
C_{1-6} alkylaryl-$SO_2(CH_2)_r$-,
C_{1-6} alkoxy,
aryl C_{1-6} alkoxy,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
arylamino,
arylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino,
aryl C_{1-6} alkylamino C_{1-6} alkyl,

arylcarbonyloxy,
aryl C_{1-6} alkylcarbonyloxy,
C_{1-6} dialkylamino,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl,
arylsulfonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonylamino,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl,
C_{1-8} alkoxycarbonylamino,
C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
aryloxycarbonylamino C_{1-8} alkyl,
aryl C_{1-8} alkoxycarbonylamino,
aryl C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
C_{1-8} alkylcarbonylamino,
C_{1-8} alkylcarbonylamino C_{1-6} alkyl,
arylcarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonylamino,
aryl C_{1-6} alkylcarbonylamino C_{1-6} alkyl,
aminocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonylamino,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
arylaminocarbonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonylamino,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
aminosulfonylamino C_{1-6} alkyl,
C_{1-8} alkylaminosulfonylamino,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
arylaminosulfonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminosulfonylamino,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
C_{1-6} alkylsulfonyl,
C_{1-6} alkylsulfonyl C_{1-6} alkyl,
arylsulfonyl C_{1-6} alkyl,

aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl,
C_{1-6} alkylcarbonyl,
C_{1-6} alkylcarbonyl C_{1-6} alkyl,
arylcarbonyl C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonyl,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl,
C_{1-6} alkylthiocarbonylamino,
C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
arylthiocarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylthiocarbonylamino,
aryl C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
arylaminocarbonyl C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonyl, or
aryl C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
wherein the alkyl or N atoms may be unsubstituted or substituted with one or more substituents selected from R^{21} and R^{22}; or R^8 and R^9 are combined to form oxo;

R^{10} and R^{11} are each independently selected from
hydrogen,
aryl,
halogen,
aryl-$(CH_2)_p$-,
hydroxyl,
C_{1-8} alkylcarbonylamino,
aryl C_{1-5} alkoxy,
C_{1-5} alkoxycarbonyl,
aminocarbonyl,
C_{1-8} alkylaminocarbonyl,
C_{1-6} alkylcarbonyloxy,
C_{3-8} cycloalkyl,
amino,

C_{1-6} alkylamino,
amino C_{1-6} alkyl,
arylaminocarbonyl,
aryl C_{1-5} alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl C_{1-6} alkyl,
hydroxycarbonyl,
hydroxycarbonyl C_{1-6} alkyl,
C_{1-8} alkyl, either unsubstituted or substituted, with one or more groups selected from: halogen, hydroxyl, C_{1-5} alkylcarbonylamino, aryl C_{1-5} alkoxy, C_{1-5} alkoxycarbonyl, aminocarbonyl, C_{1-5} alkylaminocarbonyl, C_{1-5} alkylcarbonyloxy, C_{3-8} cycloalkyl, oxo, amino, C_{1-3} alkylamino, amino C_{1-3} alkyl, arylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, aminocarbonyl, aminocarbonyl C_{1-4} alkyl, hydroxycarbonyl, or hydroxycarbonyl C_{1-5} alkyl,
$HC{\equiv}C(CH_2)_r$ -
C_{1-6} alkyl-$C{\equiv}C(CH_2)_r$ -,
C_{3-7} cycloalkyl-$C{\equiv}C(CH_2)_r$ -,
aryl-$C{\equiv}C(CH_2)_r$ -,
C_{1-6} alkylaryl-$C{\equiv}C(CH_2)_r$ -,
$H_2C{=}CH(CH_2)_r$ -,
C_{1-6} alkyl-$CH{=}CH(CH_2)_r$ -,
C_{3-7} cycloalkyl-$CH{=}CH(CH_2)_r$ -,
aryl-$CH{=}CH(CH_2)_r$-,
C_{1-6} alkylaryl-$CH{=}CH(CH_2)_r$ -,
C_{1-6} alkyl-$SO_2(CH_2)_r$-,
C_{1-6} alkylaryl-$SO_2(CH_2)_r$-,
C_{1-6} alkoxy,
aryl C_{1-6} alkoxy,
aryl C_{1-6} alkyl,
C_{1-6} alkylamino C_{1-6} alkyl,
arylamino,

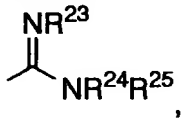
arylamino C_{1-6} alkyl,
aryl C_{1-6} alkylamino,
aryl C_{1-6} alkylamino C_{1-6} alkyl,
arylcarbonyloxy,
aryl C_{1-6} alkylcarbonyloxy,
C_{1-6} dialkylamino,
C_{1-6} dialkylamino C_{1-6} alkyl,
C_{1-6} alkylaminocarbonyloxy,
C_{1-8} alkylsulfonylamino,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl,
arylsulfonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonylamino,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl,
C_{1-8} alkoxycarbonylamino,
C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
aryloxycarbonylamino C_{1-8} alkyl,
aryl C_{1-8} alkoxycarbonylamino,
aryl C_{1-8} alkoxycarbonylamino C_{1-8} alkyl,
C_{1-8} alkylcarbonylamino,
C_{1-8} alkylcarbonylamino C_{1-6} alkyl,
arylcarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonylamino,
aryl C_{1-6} alkylcarbonylamino C_{1-6} alkyl,
aminocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonylamino,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
arylaminocarbonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonylamino,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl,
aminosulfonylamino C_{1-6} alkyl,
C_{1-8} alkylaminosulfonylamino,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
arylaminosulfonylamino C_{1-6} alkyl,
aryl C_{1-8} alkylaminosulfonylamino,

aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl,
C_{1-6} alkylsulfonyl,
C_{1-6} alkylsulfonyl C_{1-6} alkyl,
arylsulfonyl C_{1-6} alkyl,
aryl C_{1-6} alkylsulfonyl,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl,
C_{1-6} alkylcarbonyl,
C_{1-6} alkylcarbonyl C_{1-6} alkyl,
arylcarbonyl C_{1-6} alkyl,
aryl C_{1-6} alkylcarbonyl,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl,
C_{1-6} alkylthiocarbonylamino,
C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
arylthiocarbonylamino C_{1-6} alkyl,
aryl C_{1-6} alkylthiocarbonylamino,
aryl C_{1-6} alkylthiocarbonylamino C_{1-6} alkyl,
C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
arylaminocarbonyl C_{1-6} alkyl,
aryl C_{1-8} alkylaminocarbonyl,
aryl C_{1-8} alkylaminocarbonyl C_{1-6} alkyl,
C_{7-20} polycyclyl C_{0-8} alkylsulfonylamino C_{0-6} alkyl,
C_{7-20} polycyclyl C_{0-8} alkylcarbonylamino C_{0-6} alkyl,
C_{7-20} polycyclyl C_{0-8} alkylaminosulfonyolamino C_{0-6} alkyl,
C_{7-20} polycyclyl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl, or
C_{7-20} polycyclyl C_{0-8} alkyloxycarbonylamino C_{0-6} alkyl
wherein the alkyl or N atoms may be unsubstituted or substituted with one or more substituents selected from R^{21} and R^{22}, wherein the polycyclyl may be unsubstituted or substituted with R^{31}, R^{32}, R^{33} and R^{34}, and provided that the carbon atom to which R^{10} and R^{11} are attached is itself attached to no more than one heteroatom; or R^{10} and R^{11} are combined to form oxo;

R^{12} is selected from
hydroxy,

C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{0-8} alkylcarbonyloxy C_{1-4} alkyloxy,
C_{1-6} dialkylaminocarbonylmethyloxy,
aryl C_{1-6} dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C_{1-6} alkyl; and

R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from
hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
thio,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
aryl C_{0-6} alkylamino C_{0-6} alkyl,
C_{1-4} alkoxyamino C_{0-8} alkyl,
hydroxy C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{1-6} alkylamino C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,



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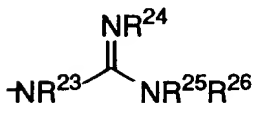


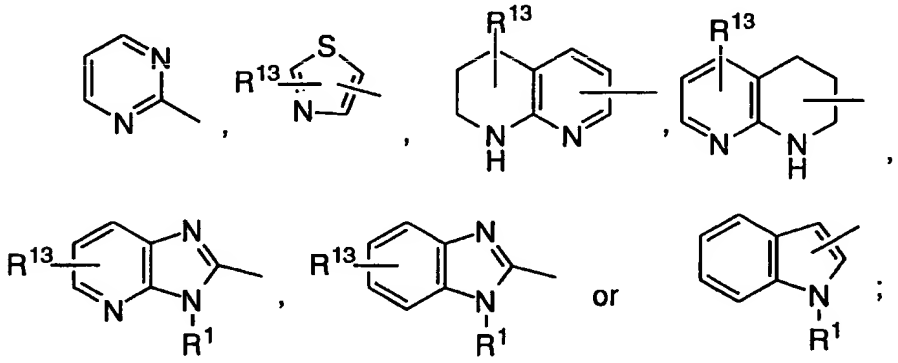
; or R^{13}, R^{14}, R^{15} and R^{16}

are combined to form oxo;

R^{31}, R^{32}, R^{33} and R^{34} are each independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, oxo, aryl, aryl C_{1-8} alkyl, amino, amino C_{1-8} alkyl, C_{1-3} acylamino, C_{1-3} acylamino C_{1-8} alkyl, C_{1-6} alkylamino, C_{1-6} alkylamino-C_{1-8} alkyl, C_{1-6} dialkylamino, C_{1-6} dialkylamino C_{1-8} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-3} alkoxycarbonyl, C_{1-3} alkoxycarbonyl C_{1-6} alkyl, hydroxycarbonyl-C_{1-6} alkyloxy, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, trifluoroethoxy, C_{1-8} alkyl-$S(O)_q$, C_{1-8} alkylaminocarbonyl, C_{1-8} dialkylaminocarbonyl, C_{1-8} alkyloxycarbonylamino, C_{1-8} alkylaminocarbonyloxy or C_{1-8}alkylsulfonylamino;

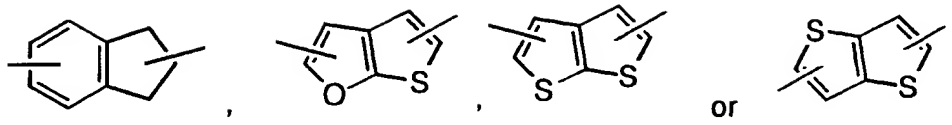
provided that Ring is not a 6-membered monocyclic aromatic ring;

provided further that when Ring is thiophene, then X is selected from

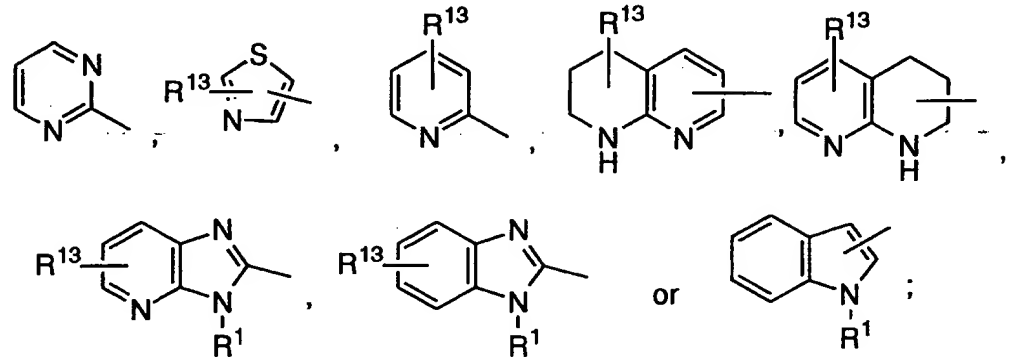


;

provided further that when Ring is selected from isoxazole, isoxazoline, imidazole, imidazoline, benzofuran, benzothiophene, benzimidazole, indole, benzothiazole, benzoxazole,



then X is selected from

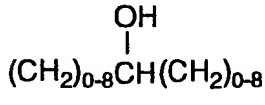


and the pharmaceutically acceptable salts thereof.

2. The compound of Claim 1, wherein

Y is selected from

C_{0-8} alkylene,
C_{3-10} cycloalkyl,
C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,
C_{0-8} alkylene-$CONR^5$-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-$S(O)_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene,
C_{0-8} alkylene-CO-C_{0-8} alkylene,
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-$(CH_2)_{0-6}$,
$(CH_2)_{0-6}$ aryl-CO-NH-$(CH_2)_{0-6}$, or



;

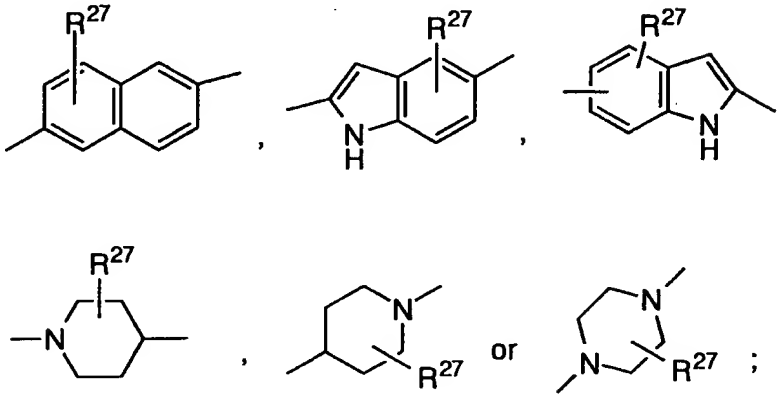
Z is $(CH_2)_m$ where m is zero; and

and the pharmaceutically acceptable salts thereof.

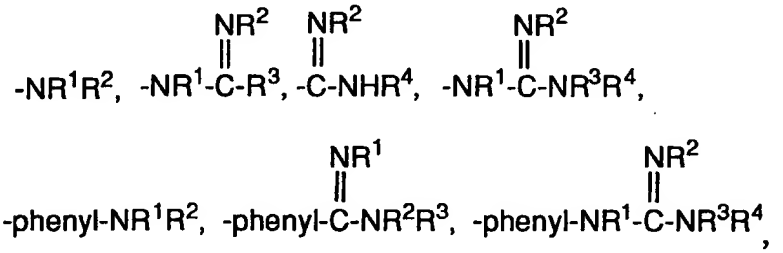
3. The compound of Claim 2, of the formula

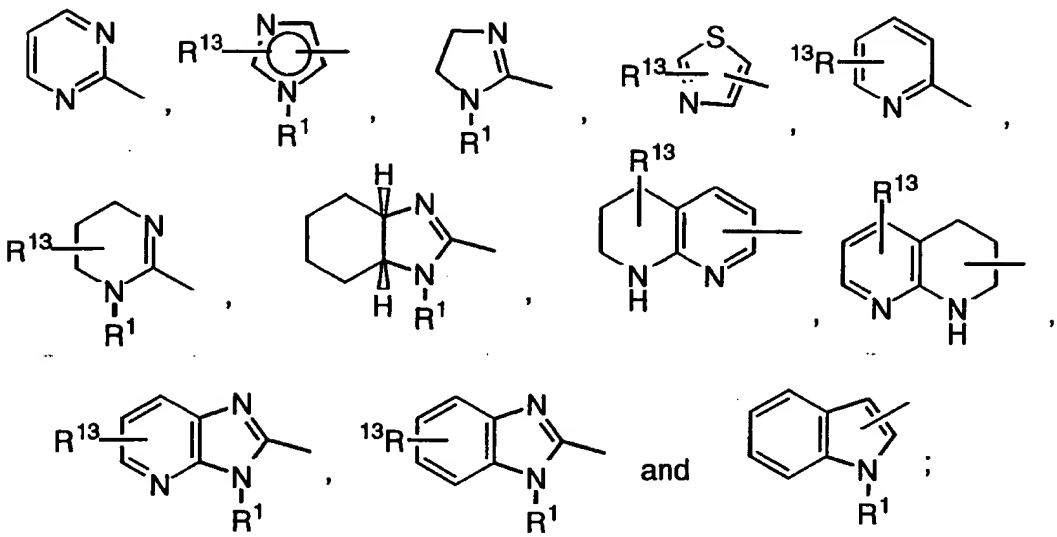
X-Y-Ring-A-B

wherein Ring is selected from



X is selected from





Y is selected from

C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-CO-C_{0-8} alkylene,
C_{0-8} alkylene-$CONR^5$-C_{0-8} alkylene,
C_{0-8} alkylene-O-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-$S(O)_{0-2}$-C_{0-8} alkylene,
C_{0-8} alkylene-SO_2-NR^5-C_{0-8} alkylene,
C_{0-8} alkylene-NR^5-SO_2-C_{0-8} alkylene or
$(CH_2)_{0-6}$ aryl$(CH_2)_{0-6}$;

A is selected from

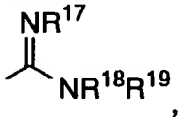
$O(CH_2)_p$, $NR^6(CH_2)_p$, $\overset{O}{\overset{\|}{C}}NR^{29}(CH_2)_p$, $NR^{29}\overset{O}{\overset{\|}{C}}(CH_2)_p$, $\overset{O}{\overset{\|}{C}}(CH_2)_p$,

$SO_2(CH_2)_p$, $SO_2NR^{29}(CH_2)_p$, $NR^{29}SO_2(CH_2)_p$ or $C\equiv C-(CH_2)_p$;

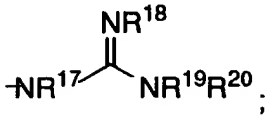
where p is an integer from 0 to 3;

R^1, R^2, R^3, R^4, R^5, R^6, R^{17}, R^{18}, R^{19}, R^{20}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27} and R^{29} are each independently selected from

hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{0-6} alkyl,



, or



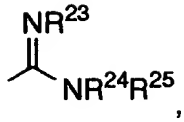
;

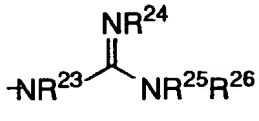
R^{10} and R^{11} are each independently selected from
hydrogen,
fluorine,
C_{1-8} alkyl,
hydroxyl,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,

C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminosulfonylamino C_{0-6} alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl or
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl;

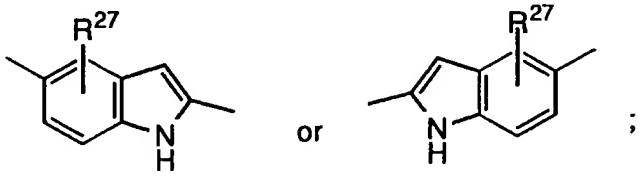
R^{12} is selected from
hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy or
aryl C_{0-8} alkylcarbonyloxy C_{1-4} alkyloxy;

R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from
hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy,
hydroxy C_{0-6} alkyl,

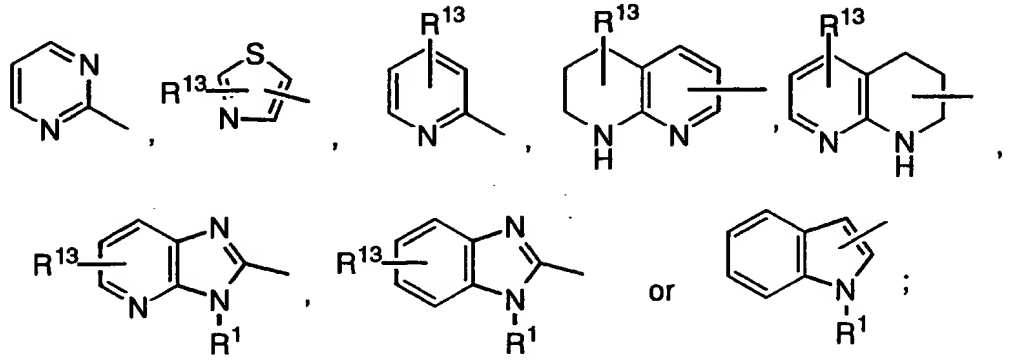

, or


; or R^{13}, R^{14}, R^{15} and R^{16} are combined to form oxo;

provided that when Ring is

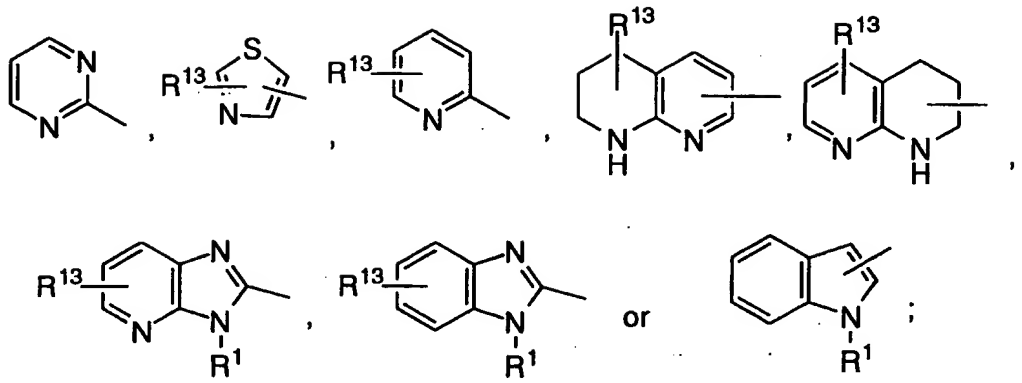

;

then X is selected from



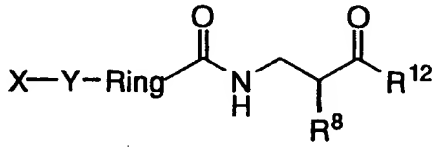
and the pharmaceutically acceptable salts thereof.

4. The compound of Claim 3, wherein X is selected from

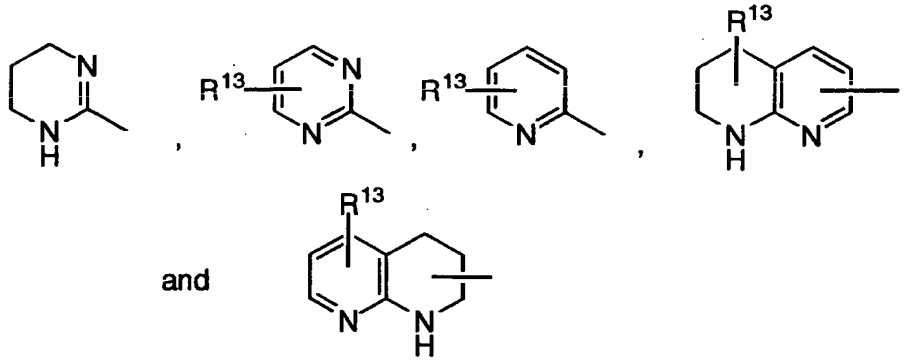


and the pharmaceutically acceptable salts thereof.

5. The compound of Claim 4, of the formula



X is selected from



Y is selected from

C_{0-8} alkylene,

C_{0-8} alkylene-NR^5-C_{0-8} alkylene; and

R^{12} is selected from

hydroxy or

C_{1-8} alkyloxy;

and the pharmaceutically acceptable salts thereof .

6. The compound of Claim 5, selected from

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester;

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)carbonyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine ethyl ester;

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine; or

6-[(1,4,5,6-Tetrahydropyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

and the pharmaceutically acceptable salts thereof.

7. The compound of Claim 6, selected from

[6-(5,6,7,8-Tetrahydro-[1,8]-naphthyridin-2-yl)naphthylen-2-yl]-carbonyl-2(S)-phenylsulfonylamino-β-alanine;

6-([N-Pyridin-2-yl)aminomethyl)naphthylen-2-yl)carbonyl-2(S)-phenylsulfonylamino-β-alanine;

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)piperidin-1-yl-carbonyl-2(S)-phenylsulfonylamino-β-alanine; or

6-[(Pyrimidinyl-2-yl)aminomethyl]naphthylen-2-yl-carbonyl-2(S)-phenylsulfonyl-β-alanine;

and the pharmaceutically acceptable salts thereof.

8. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition made by combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

10. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

11. A method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

12. The method of Claim 11, wherein the vitronectin antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of angiogenesis, inhibition of diabetic retinopathy, inhibition of macular degeneration or inhibition of tumor growth.

13. The method of Claim 12, wherein the vitronectin antagonizing effect is the inhibition of bone resorption.

14. A method of treating or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

15. The method of Claim 14, wherein the condition is selected from the group consisting of osteoporosis and cancer.

16. The method of Claim 15, wherein the condition is osteoporosis.

17. A method of inhibiting bone resorption in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

18. A method of treating osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

19. A method of preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

20. A method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

21. A method of treating or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

22. A method of inhibiting bone resorption in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

23. A method of treating osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

24. A method of preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

25. The use of the compound of Claim 1 in the preparation of a medicament for the treatment or prevention of a condition selected from: osteoporosis, bone resorption, tumor growth, cancer, restenosis, artherosclerosis, diabetic retinopathy, macular degeneration or angiogenesis in a mammal in need thereof.

26. A drug which is useful for treating or preventing a condition selected from: osteoporosis, bone resorption, tumor growth, cancer, restenosis, artherosclerosis, diabetic retinopathy, macular degeneration or angiogenesis in a mammal in need thereof, the effective ingredient of the said drug being the compound of Claim 1.

27. A method of treating tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 and one or more agents known to be cytotoxic or antiproliferative.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/32710 A1 (MERCK & CO., INC.) 07 December 1995, claims 1-25.	1-27
A	US 5,416,099 A (HARTMAN et al.) 16 May 1995, claims 1-6.	1-27
A	XUE, C-B. et al. Design, synthesis and in vitro activities of a series of benzimidazole/benzoxazole glycoprotein IIb/IIIa inhibitors. Biorg. & Medic. Chem. Lett. 1996, Volume 6, No. 3, pages 339-344, especially tables 1 and 2 on pages 342 and 343.	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
20 JANUARY 1998	23 FEB 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHANA AULAKH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19349

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/18, 31/19, 31/44, 31/47, 31/195, 31/405, 31/415, 31/425, 31/435, 31/505; C07C 63/00, 307/06, 307/08, 307/10; C07D 209/40, 213/89, 217/08, 233/44, 233/88, 239/08, 239/14, 239/42

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/275, 300, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/323, 332; 546/118, 122, 143, 290, 291, 301, 304, 309, 310, 311, 312; 548/195, 300.1, 308.4, 335.5, 495; 560/34; 564/86, 147

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/275, 300, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/323, 332; 546/118, 122, 143, 290, 291, 301, 304, 309, 310, 311, 312; 548/195, 300.1, 308.4, 335.5, 495; 560/34; 564/86, 147

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. The species are as follows:
I. Compounds of formula of claim 1 where Ring or X is 6-membered hetero ring containing O, S and N as the heteroatoms, classifiable in class 544, subclass 2+.

II. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing O and N as the heteroatoms, classifiable in class 544, subclass 63+.

III. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing four N as the heteroatoms, classifiable in class 544, subclass 179.

IV. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing three N as the heteroatoms, classifiable in class 544, subclass 180.

V. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing two N as the heteroatoms, classifiable in class 544, subclass 224+.

VI. Compounds of formula of claim 1 where Ring or X is a 6-membered hetero ring containing only one N as the heteroatom, classifiable in class 546, subclass 26+.

VII. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing O, S and N as the heteroatoms, classifiable in class 548, subclass 122+.

VIII. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing four N as the heteroatoms, classifiable in class 548, subclass 250+.

IX. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing three N as the heteroatoms, classifiable in class 548, subclass 255+.

X. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing two N as the heteroatoms, classifiable in class 548, subclass 300.1+.

XI. Compounds of formula of claim 1 where Ring or X is a 5-membered hetero ring containing only one N as the heteroatom, classifiable in class 548, subclass 400+.

XII. Compounds of formula of claim 1 where Ring or X is a hetero ring containing only S as the heteroatoms, classifiable in class 549, subclass 1+.

XIII. Compounds of formula of claim 1 where Ring or X is a hetero ring containing only O as the heteroatoms, classifiable in class 549, subclass 200+.

XIV. Compounds of formula of claim 1 containing carboxylic acid ester and either Ring or X is not a hetero ring, classifiable in class 560, subclass 11+.

XV. Compounds of formula of claim 1 containing amino nitrogen and either Ring or X is not a hetero ring, classifiable in class 564, subclass 1+.

The claims are deemed to correspond to the species listed above in the following manner:

Species V and VI. Claims 6 and 7.

The following claims are generic: Claims 1-5 and 8-27.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

There is no common core Which in the Markush Practice, is a significant structural element shared by all the alternatives; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1) and further, all alternatives do not belong to a recognized class of chemical compounds in the art to which the invention pertains; see supra (B) (2).